Barrett's esophagus: Surveillance and management

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INTRODUCTION

In Barrett's esophagus, metaplastic columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus [1,2]. The metaplastic epithelium is acquired as a consequence of chronic gastroesophageal reflux disease and predisposes to cancer development.

This topic will review the management of Barrett's esophagus, including the approach to surveillance. The pathogenesis, clinical manifestations, and diagnosis of Barrett's esophagus are discussed separately. (See "Barrett's esophagus: Pathogenesis and malignant transformation" and "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis".)

The management of Barrett's esophagus has been addressed in several society guidelines, including a guideline from the American College of Gastroenterology [3], a guideline from the British Society of Gastroenterology [4], guidelines from the American Society of Gastrointestinal Endoscopy [5,6], and a guideline and expert review from the American Gastroenterological Association [7,8]. In addition, a consensus statement on Barrett's esophagus by an international group of experts has been published [9]. The discussion that follows is generally consistent with these guidelines. However, it should be noted that many of the issues related to the surveillance and management of Barrett's esophagus remain controversial, with considerable disagreement among experts [7,10].

CANCER RISK

Cancer incidence and mortality — Estimates of the annual cancer incidence in patients with Barrett's esophagus have ranged from 0.1 to almost 3.0 percent, with other studies suggesting rates closer to 0.1 to 0.4 percent per year [11-27]. Although the risk of developing esophageal cancer is increased at least 30-fold above that of the general population, the absolute risk of developing cancer for an individual patient with nondysplastic Barrett's esophagus is low [23]. The risk of developing cancer is higher among males, older patients, and patients with long segments of Barrett's mucosa [19,25,26,28-30].

Patients with Barrett's esophagus most often die from causes unrelated to esophageal cancer. This is likely because many patients with Barrett's esophagus are older, overweight, and succumb to common diseases, such as coronary artery disease, before developing esophageal adenocarcinoma. In a meta-analysis with 50 studies that included 14,109 patients, the mortality rate due to esophageal adenocarcinoma was 3.0 per 1000 person-years, whereas the mortality rate due to other causes was 37.1 per 1000 person-years [24].

Dysplasia as a marker of risk — Traditionally, esophageal adenocarcinomas (EACs) in patients with Barrett's esophagus have been assumed to evolve through a gradual sequence of genetic alterations that are associated with dysplastic changes of progressive severity. This slow progression to cancer has been thought to provide adequate time for surveillance to detect dysplasia that can be eradicated endoscopically before it becomes malignant. However, subsequent data suggest that approximately 40 percent of EACs evolve through this traditional pathway and that 60 percent of EACs develop from chromosomal instability in Barrett's metaplasia [31,32]. Chromosomal instability results in genomic doubling and other chromosomal alterations that can cause cancer to develop much more rapidly and perhaps even between surveillance intervals.

Few studies have documented the natural history of dysplasia, so the rate at which metaplasia progresses to dysplasia and cancer is unclear. The estimates of the risk of progression of dysplastic Barrett's esophagus to esophageal adenocarcinoma range from 0.2 to 14 percent per year and vary based on the baseline degree of dysplasia [17,28,33-44]. The reasons underlying the disparities in the reported rates of progression are unsettled, but may in part be due to referral bias and inclusion of patients with prevalent cancers in some of the reports [36,45]. The evolution of genetic changes leading from Barrett's esophagus to adenocarcinoma is discussed in more detail, separately. (See "Barrett's esophagus: Pathogenesis and malignant transformation", section on 'Malignant transformation'.)

A meta-analysis that included 24 studies with 2694 patients who had low-grade dysplasia found that esophageal adenocarcinoma developed in 119 patients (4 percent) [33]. The pooled incidence rate for the development of esophageal adenocarcinoma was 0.54 percent per year (95% CI 0.32-0.76 percent). For the combined outcome of esophageal adenocarcinoma or high-grade dysplasia, the incidence rate was 1.73 percent per year.

Based on available reports, we estimate the following rates of progression to esophageal adenocarcinoma [17,28,33-43]:

- General population of patients with Barrett's esophagus – 0.25 percent per year.
- Low-grade dysplasia – The risk of cancer is poorly defined because there are large disparities among studies on the natural history of low-grade dysplasia. The reasons underlying these disparities are not entirely clear, but a major factor appears to be differences in how study pathologists diagnose low-grade dysplasia. "Expert" pathologists will usually downgrade a diagnosis of low-grade dysplasia made by community pathologists [38]. A meta-analysis estimates that patients with low-grade dysplasia progress to cancer at the rate of 0.54 percent per year [33], but the range of reported cancer risk is so high that precise estimates of cancer risk are not possible [34,43].
- Indefinite for dysplasia – As with low-grade dysplasia, the risk of cancer is poorly defined. Studies suggest it is between 0.2 to 1.2 percent per year [42,43,46].
- High-grade dysplasia – 4 to 8 percent per year.

Many patients with biopsies read as indefinite for dysplasia will show regression to nondysplastic Barrett's esophagus on subsequent endoscopies. In a study that included 83 patients with biopsies that were indefinite for dysplasia, 80 percent of patients had nondysplastic Barrett's esophagus on their first follow-up endoscopy [43]. However, it is possible that some of the cases of "regression" were actually due to sampling error.

SCREENING FOR BARRETT'S ESOPHAGUS

Whether to screen for Barrett's esophagus is controversial. Some groups suggest screening patients with several risk factors for developing esophageal adenocarcinoma (eg, gastroesophageal reflux disease, age >50 years, male sex, elevated body mass index with an abdominal pattern of fat distribution). Screening for Barrett's esophagus is discussed in detail elsewhere. (See "Barrett's esophagus: Epidemiology, clinical manifestations, and diagnosis", section on 'Screening patients for Barrett's esophagus'.)

GENERAL MANAGEMENT

Management of acid reflux — We typically treat all patients with Barrett's esophagus indefinitely with a proton pump inhibitor (PPI) based primarily on data from observational and in vitro studies that suggest aggressive antireflux therapy might prevent cancer [47-51]. In addition, many patients with Barrett's esophagus also have symptomatic gastroesophageal reflux disease (GERD) or endoscopic evidence of reflux esophagitis, both of which justify treatment with PPIs. We typically start patients on a PPI once daily (eg, omeprazole 20 mg daily, pantoprazole 40 mg daily), and only increase the dose if it is required to eliminate GERD symptoms or to heal reflux esophagitis. (See "Medical management of gastroesophageal reflux disease in adults", section on 'Proton pump inhibitors' and "Approach to refractory gastroesophageal reflux disease in adults", section on 'Subsequent management'.)

The primary rationale behind treating acid reflux is that it may lead to chronic esophageal inflammation, which in turn may predispose to cancer development. Refluxed acid and bile also can cause potentially carcinogenic DNA damage in Barrett's epithelial cells [52]. In a meta-analysis of 12 studies that included over 155,000 patients with Barrett's esophagus, the use of PPIs was associated with lower risk of progression to high-grade dysplasia and/or esophageal adenocarcinoma compared with no PPI (adjusted odds ratio 0.47; 95% CI 0.32-0.71) [51].

It has been suggested that patients with Barrett's esophagus are unusually resistant to PPI treatment. Esophageal pH monitoring studies frequently reveal pathologic levels of acid reflux in patients with Barrett's esophagus rendered asymptomatic by PPIs [53]. However, such resistance may be a consequence of a profound reflux diathesis rather than gastric resistance to the antisecretory effects of PPIs [54]. In other words, PPIs appear to reduce gastric acid secretion appropriately in patients with Barrett's esophagus, but the little acid that remains in the stomach refluxes into the esophagus because of the strong reflux diathesis, so pathologic levels of acid reflux persist despite considerable acid suppression. Antireflux surgery (fundoplication) is an option for highly selected patients who appear to be resistant to PPI treatment (manifest by abnormal acid reflux despite PPI therapy or nonhealing reflux esophagitis) [55], although fundoplication has not been proven to be more effective for preventing esophageal adenocarcinoma than medical therapy [56-60]. (See "Surgical treatment of gastroesophageal reflux in adults".)

Aggressive antireflux therapy may result in partial regression of the specialized intestinal metaplasia in Barrett's esophagus [61,62]. In a randomized trial, 68 patients with proven Barrett's esophagus and acid reflux were assigned to receive high-dose acid suppression (omeprazole 40 mg twice daily) or mild acid suppression (ranitidine 150 mg twice daily) [61].

Symptoms of acid reflux improved in both groups, but the degree of acid suppression was greater with omeprazole. There was a small amount of regression of Barrett's esophagus in patients who received omeprazole, but none in patients who received ranitidine. However, it is not clear that partial regression of Barrett's metaplasia means that the risk of cancer has decreased.

The Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia Trial (AspECT) evaluated the effect of high-dose PPI compared with low-dose PPI (with or without full-dose aspirin) on the time interval to reach several outcomes (all-cause mortality, esophageal carcinoma or high-grade dysplasia) [63]. Among 2557 patients with Barrett's esophagus, high-dose PPI was associated with a lower event rate and a longer time prior to the composite endpoint compared with low-dose PPI (11 versus 14 percent; time ratio 1.27, 95% CI 1.01-1.58). However, given the potential risks, additional cost, and relatively modest benefit associated with high-dose PPI, we do not routinely increase the PPI dose beyond what is needed for symptom control and healing of reflux esophagitis. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Adverse effects' and 'Other chemoprevention' below.)

Other chemoprevention — Although there is some evidence that nonsteroidal anti-inflammatory medications (including aspirin) can decrease the risk of esophageal carcinoma in patients with Barrett's esophagus, we do not routinely use them solely for the purpose of chemoprevention because of the potential for adverse effects and the low absolute risk of cancer [3]. Epidemiologic data suggest that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX) may protect against the development of Barrett's esophagus [64], or in patients with established Barrett's esophagus, the development of cancer [63,65,66]. The specialized intestinal metaplasia of Barrett's esophagus exhibits increased expression of COX-2 [67], and inhibition of COX-2 has been shown to have antiproliferative and pro-apoptotic effects in Barrett's-associated esophageal adenocarcinoma cell lines [68]. (See 'Cancer incidence and mortality' above.)

Studies that have examined the efficacy of chemoprevention in patients with Barrett's esophagus have found that the use of aspirin or NSAIDs is associated with a decrease in the risk of esophageal adenocarcinoma by approximately 40 percent [49,64,66,69-71].

In particular, aspirin appears to contribute to delaying progression of Barrett's esophagus, but the absolute risk reduction is likely low. In the Aspirin and Esomeprazole Chemoprevention in Barrett's Metaplasia Trial (AspECT) including 2557 patients with Barrett's esophagus who were followed for a median time of 8.9 years, patients were assigned to one of four different open-label treatment regimens (esomeprazole 40 mg twice daily or 20 mg once daily, with or without

full-dose aspirin) [63]. High-dose PPI with aspirin had the strongest effect for prolonging the time interval to a composite endpoint (all-cause mortality, esophageal carcinoma or high-grade dysplasia) compared with low-dose PPI without aspirin (time ratio 1.59, 95% CI 1.14-2.23). However, the difference in event rate between aspirin and no aspirin was relatively modest (11 versus 13 percent) and not statistically significant, and it is uncertain whether low-dose aspirin (which some patients with Barrett's esophagus use for prevention of cardiovascular disease) would have a similar effect. Given these uncertainties, we are not routinely using full-dose aspirin combined with high-dose PPI as chemoprevention for these patients. (See 'Management of acid reflux' above.)

The protective effect may be greater if the NSAID is combined with a statin. In a prospective study of 570 patients with Barrett's esophagus, 107 patients used a statin combined with an NSAID [70]. After a mean follow-up of 4.5 years, compared with patients using neither drug, the risk of developing adenocarcinoma or high-grade dysplasia was significantly reduced among patients using NSAIDs and statins (adjusted hazard ratio 0.22; 95% CI 0.06-0.85). The adjusted hazard ratio among the 211 patients using only an NSAID was 0.46 (95% CI 0.22-0.99). Unlike studies showing a benefit with nonselective NSAIDS, a trial of a selective COX-2 inhibitor found no benefit in preventing the progression of Barrett's esophagus to dysplasia or cancer [72].

SURVEILLANCE

Overview — The goal of surveillance is to improve outcomes by detecting dysplasia or esophageal adenocarcinoma early enough to provide effective treatment. Guidelines suggest surveillance for most patients with Barrett's esophagus, but whether surveillance is beneficial is unclear [3,4,6,7,9]. Available observational studies have not consistently shown that surveillance is beneficial. In addition, there are potential harms associated with surveillance, including a decrease in quality of life due to worry about cancer development, the risks associated with endoscopy, the risks and morbidity associated with invasive therapies used to treat lesions identified by surveillance (such as esophagectomy or radiofrequency ablation), and missed lesions despite surveillance. As a result, a well-informed patient with nondysplastic Barrett's esophagus may reasonably choose not to undergo surveillance despite endorsement of the practice by gastrointestinal societies [3]. The discussion of the risks and benefits of surveillance should be well documented in the patient's medical record, particularly if the patient elects not to undergo surveillance. If surveillance is performed, it is important to treat erosive esophagitis prior to obtaining biopsies [8].

Our approach is to perform an initial endoscopy with four-quadrant biopsies every 2 cm and wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS-3D) in

patients with suspected Barrett's esophagus (eg, salmon-colored esophageal mucosa) (picture 1). (See 'Surveillance techniques' below.)

If four-quadrant biopsies every 2 cm were not obtained at the initial endoscopy, we repeat the endoscopy within a year to obtain those biopsies. In addition, any mucosal irregularities in the Barrett's segment should be removed with endoscopic resection, and the resected specimen should be sent for evaluation by an experienced pathologist.

Our subsequent recommendations depend on whether dysplasia is present in these specimens (algorithm 1). Any diagnosis of dysplasia should be confirmed by a second pathologist with expertise in Barrett's esophagus-related neoplasia [8].

- **No dysplasia** – If the initial biopsies show no dysplasia, we discuss the potential risks and benefits of regular endoscopic surveillance with the patient. The length of the nondysplastic Barrett's segment generally informs surveillance intervals, and this approach is supported by society guidelines [3]. Patients with longer segments (≥3 cm) undergo surveillance every three years, whereas patients with shorter segments (<3 cm) undergo surveillance every five years.

- **Indefinite for dysplasia** – If the initial biopsies are indefinite for dysplasia, we recommend optimizing medical antireflux therapy (eg, prescribing a proton pump inhibitor [PPI] twice daily, ensuring compliance with PPI therapy, ensuring that the PPI is taken correctly). Antireflux therapy minimizes reactive esophageal changes due to reflux esophagitis that may be mistaken for dysplastic changes. After antireflux therapy has been optimized, we repeat an endoscopy with biopsy specimens taken every 1 cm. We typically perform the endoscopy after two months of treatment (to allow sufficient time for healing). Repeat endoscopy should not be delayed beyond six months. Any mucosal irregularities should be removed with endoscopic resection.

  If the repeat biopsies still are indefinite for dysplasia, the diagnosis should be confirmed by a pathologist with expertise in esophageal histopathology. If the diagnosis is confirmed, management options include surveillance endoscopy every 12 months or referral of the patient to a center with expertise in managing patients with Barrett's esophagus.

- **Low-grade dysplasia, high-grade dysplasia, or intramucosal carcinoma** – If the biopsies show dysplasia or intramucosal carcinoma, we suggest that the diagnosis be confirmed by another pathologist with expertise in Barrett's esophagus-related neoplasia. Endoscopy should be repeated as soon as feasible if four-quadrant biopsy specimens were not obtained at 1 cm intervals or if there were any mucosal irregularities that were not

removed with endoscopic resection. Endoscopists who do not perform endoscopic resection should refer patients with mucosal irregularities to specialty centers for that procedure prior to proceeding with endoscopic eradication therapy. Endoscopic resection of mucosal irregularities is required to accurately assess the grade of dysplasia.

We generally recommend endoscopic eradication therapy for patients who are confirmed to have high-grade dysplasia or intramucosal carcinoma, and who have no evidence of submucosal invasion in their resected specimens. (See 'High-grade dysplasia or intramucosal carcinoma' below.)

Some guidelines recommend either surveillance or endoscopic eradication for patients with low-grade dysplasia [4,7,9]. In patients who elect to undergo endoscopic eradication, endoscopic radiofrequency ablation is preferable for preventing progression of dysplasia. If endoscopic surveillance is the chosen approach for low-grade dysplasia, patients should have biopsies obtained every 1 cm, any mucosal irregularities should be removed with endoscopic resection, and surveillance should be performed every 6 months for one year and then annually until there is reversion to nondysplastic Barrett's [8]. (See 'Low-grade dysplasia' below.)

Efficacy of surveillance — Observational studies suggest that surveillance can detect curable dysplasia in Barrett's esophagus and that asymptomatic cancers discovered during surveillance are less advanced than those found in patients who present with symptoms such as dysphagia or weight loss [73-79]. However, these studies are susceptible to biases such as lead-time bias and length-time bias. (See "Evidence-based approach to prevention", section on 'Special biases'.)

Findings that call into question the value of surveillance include:

- Documented development of incurable malignancies in patients who were adherent to endoscopic surveillance programs [73,74].
- A case-control study with 70 cases and 101 controls that found that patients with esophageal cancer in the setting of Barrett's esophagus were as likely to have undergone endoscopic surveillance as patients with Barrett's esophagus but no cancer [80].

A multicenter randomized trial is being conducted to look at whether endoscopic surveillance every two years influences outcomes such as overall survival, cancer-specific survival, and stage at diagnosis of esophageal adenocarcinoma in patients with nondysplastic Barrett's esophagus or Barrett's esophagus with low-grade dysplasia [81].

Surveillance techniques — The endoscopic surveillance of Barrett's esophagus should include a careful inspection of the Barrett's epithelium with high-resolution white light endoscopy and with chromoendoscopy (including virtual chromoendoscopy). Adequate time should be spent inspecting the Barrett's esophagus segment and the gastric cardia in retroflexion. Any visible abnormalities should be removed with endoscopic resection. In addition, random four-quadrant biopsies should be obtained every 2 cm (every 1 cm in patients with known or suspected dysplasia). This biopsy protocol is referred to as the Seattle biopsy sampling protocol [6].

Dysplasia in Barrett's esophagus is often patchy in extent and severity, and dysplastic areas can easily be missed because of biopsy sampling error [82-85]. Careful inspection of the metaplastic area and extensive biopsy sampling can reduce sampling error but cannot eliminate the problem entirely [86-88]. In addition, even when dysplasia is detected, foci of invasive cancer can be missed. In a meta-analysis of studies with patients who had esophagectomies for high-grade dysplasia with no apparent tumor mass, 13 percent of the resection specimens had invasive cancer [84]. In a subsequent study of 68 patients undergoing esophagectomy for high-grade dysplasia, 12 patients (18 percent) had adenocarcinoma detected in the resected esophagus [85]. Four of the cancers were intramucosal, and eight were invasive (extending into the submucosa).

Several advanced endoscopic techniques have been proposed to enhance the identification of dysplastic areas for biopsy sampling [89-94]. These techniques include mucosal staining with vital dyes (chromoendoscopy), endosonography, optical coherence tomography, confocal endomicroscopy, and virtual chromoendoscopy using narrow band imaging (NBI) or a similar technique. Some society guidelines recommend routine use of advanced imaging techniques such as chromoendoscopy, including virtual chromoendoscopy [6]. (See "Chromoendoscopy" and "Barrett's esophagus: Evaluation with optical chromoscopy" and "Confocal laser endomicroscopy and endocytoscopy", section on 'Barrett's esophagus'.)

A meta-analysis of 14 studies with a total of 843 patients examined whether advanced imaging techniques can increase the detection of dysplasia or cancer relative to white light endoscopy with random biopsies [95]. The investigators found that advanced imaging techniques increased the diagnostic yield for dysplasia or cancer by 34 percent (95% CI 20 to 56 percent). The increase in yield was similar for chromoendoscopy and virtual chromoendoscopy (eg, NBI). However, whether this increase in diagnostic yield leads to improved patient outcomes is unclear.

Wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS-3D) has been proposed as a method to improve the detection of dysplasia during endoscopic surveillance of Barrett's esophagus, and the use of WATS-3D (in addition to Seattle protocol

biopsy sampling) for surveillance is supported by some guidelines [6]. WATS-3D involves abrasive brushing of Barrett's metaplasia followed by computerized neural network analysis of the brush specimen to identify neoplasia. In a study of 160 patients with Barrett's metaplasia undergoing surveillance endoscopy, the detection rate for high-grade dysplasia (HGD)/adenocarcinoma (EAC) was higher with WATS-3D combined with biopsy sampling compared with biopsy sampling alone (18 versus 4 percent; absolute difference 14 percent, 95% CI 8-21) [96]. Of note, one case of HGD/EAC was missed in the group with WATS-3D combined with biopsy sampling, whereas 23 cases of HGD/EAC were missed by biopsy sampling alone. In another study of 12,899 patients undergoing endoscopies in which both standard forceps biopsies and WATS samples were taken, forceps biopsies identified dysplasia in 88 patients, while WATS identified an additional 213 cases of dysplasia, increasing the dysplasia detection rate from 0.68 to 2.33 percent [97].

A number of molecular markers for cancer risk have been proposed as alternatives to random biopsy sampling to detect dysplasia in Barrett's esophagus [98-101]. Promising molecular markers that have been associated with carcinogenesis in Barrett's esophagus include abnormalities in p53 and cyclin D1 expression, and abnormal cellular DNA content demonstrable by flow cytometry or methylation arrays. Additional evaluation of the markers is needed before they can be recommended for routine clinical use or to replace random biopsies [7]. However, some markers may serve as an adjunct to established diagnostic methods. For example, the British Society of Gastroenterology suggests that immunostaining of esophageal biopsies for p53 may improve the reproducibility of a diagnosis of dysplasia [4].

MANAGEMENT OF DYSPLASIA OR INTRAMUCOSAL CARCINOMA

Dysplasia in Barrett's esophagus was traditionally managed with esophagectomy, a procedure associated with considerable morbidity and mortality. Subsequently, dysplasia is usually managed with endoscopic eradication therapy, which includes the use of endoscopic ablation techniques and/or endoscopic resection (ER) (algorithm 1). Any diagnosis of dysplasia should be confirmed by a second pathologist with expertise in esophageal pathology [3].

Endoscopic ablation techniques have used thermal or photochemical energy to destroy Barrett's mucosa and do not provide a tissue specimen for histologic analysis. ER uses a diathermic snare to remove a segment of Barrett's mucosa and submucosa, and the removed tissue is submitted for histological examination. Thus, ER can be therapeutic and can provide invaluable information regarding the depth of tumor involvement (T stage). In addition, areas of mucosal irregularities in the setting of Barrett's esophagus are treated with ER. The frequency of metachronous neoplasia appears to be reduced if all Barrett's metaplasia is eradicated, not

just the dysplastic areas, and the goal of modern endoscopic therapy for dysplasia is to eradicate both dysplastic and nondysplastic Barrett's metaplasia completely. The term "endoscopic eradication therapy" encompasses the use of endoscopic ablation and/or endoscopic resection to achieve that goal.

Low-grade dysplasia — For patients found to have low-grade dysplasia, biopsy specimens should be obtained at 1 cm intervals and any mucosal irregularities should be removed with endoscopic resection. If biopsy specimens were not obtained at 1 cm intervals or a mucosal irregularity was not removed with endoscopic resection, endoscopy should be repeated as soon as possible to obtain these specimens. A finding of low-grade dysplasia on biopsies should be confirmed by a pathologist with expertise in esophageal histopathology because low-grade dysplasia in Barrett's esophagus is not diagnosed reliably [7]. If a diagnosis of low-grade dysplasia is confirmed, we perform endoscopic eradication therapy with radiofrequency ablation (RFA) [8].

Although guidelines allow either surveillance or endoscopic eradication for patients with low-grade dysplasia, studies suggest that RFA may be a preferable alternative in patients who are willing to accept the risks of the procedure [102]. Alternative methods to achieve eradication include spray cryotherapy and endoscopic resection of the entire segment of Barrett's mucosa, but RFA is the preferred ablation technique. If the patient does not undergo endoscopic eradication therapy, surveillance endoscopy should be performed every six months for one year and then annually until there is reversion to nondysplastic Barrett's [8]. Four quadrant biopsies should be obtained at 1 cm intervals. (See 'Endoscopic ablative therapies' below and 'Endoscopic resection' below.)

Studies show that RFA decreases the risk of progression to high-grade dysplasia or adenocarcinoma compared with surveillance [102,103]. In a meta-analysis of eight studies including 619 patients with low-grade dysplasia, patients treated with RFA were less likely to progress to high-grade dysplasia or cancer compared with patients in a surveillance program (OR 0.07, 95% CI 0.02-0.22) [103]. However, there remain unanswered questions regarding the durability of the ablation procedure and the need for endoscopic surveillance after ablation for low-grade dysplasia [104,105]. (See "Barrett's esophagus: Treatment with radiofrequency ablation", section on 'Follow-up endoscopy'.)

High-grade dysplasia or intramucosal carcinoma — For patients found to have high-grade dysplasia or intramucosal carcinoma, biopsy specimens should be obtained at 1 cm intervals, and any mucosal irregularities should be removed with ER. If biopsy specimens were not obtained at 1 cm intervals or a mucosal irregularity was not removed with endoscopic resection, endoscopy should be repeated as soon as possible to obtain these specimens. Factors that

should be considered when choosing a treatment for high-grade dysplasia and intramucosal cancer in Barrett's esophagus include:

- The patient's age and life expectancy
- The patient's comorbidities
- The extent of dysplasia (short segments of Barrett's esophagus are easier to ablate than longer segments with multifocal dysplasia)
- Local expertise in surgery and endoscopy
- The patient's preferences with regard to undergoing surgery, undergoing repeated endoscopies, and accepting the possibility of recurrent neoplasia in the absence of esophagectomy

Most patients with high-grade dysplasia or intramucosal carcinoma should undergo endoscopic eradication therapy with the goal of removing all of the dysplastic and nondysplastic metaplastic tissue [4,5,7,9,106]. Any visible mucosal irregularities should be removed by ER, and the specimen sent for histologic evaluation prior to ablation therapy. If the resected specimen shows invasion of the submucosa, endoscopic therapy is generally not advised. (See 'Management of invasive esophageal adenocarcinoma' below.)

Our preference for endoscopic eradication following ER of any visible lesions is RFA because it is effective and has a good safety profile. Generally, esophagectomy is no longer used as first-line treatment for dysplasia, and its use is limited to special circumstances such as failure to eliminate dysplasia with multiple sessions of endoscopic eradication therapy. The frequency of surveillance will depend on whether all intestinal metaplasia is eradicated. (See "Barrett's esophagus: Treatment with radiofrequency ablation", section on 'Follow-up endoscopy'.)

All treatment approaches are associated with risks and unclear long-term benefits. Relatively few studies on treatments for dysplasia in Barrett's esophagus have followed patients for more than five years. As a result, the long-term efficacy of these therapies in reducing cancer deaths is not established, although at least two cost-effectiveness analyses concluded that endoscopic ablation provided the longest quality-adjusted life expectancy [107,108].

Endoscopic ablative therapies — Endoscopic ablative therapies use thermal or radiofrequency energy to ablate the abnormal epithelium in Barrett's esophagus [109-112]. The most commonly used modality is RFA. However, noncontact methods (such as cryoablation) occasionally may be needed in patients with a tortuous esophagus or strictures.

The effectiveness of endoscopic therapy was examined in a retrospective study of 166 patients with high-grade dysplasia or early cancer [113]. Patients were treated with PDT, RFA, and/or argon plasma coagulation. In addition, endoscopic resection was performed for focal nodular

Barrett's esophagus, for limited expanses of flat Barrett's esophagus, and for focal residual Barrett's esophagus following ablative therapy. Complete eradication of neoplasia was achieved in 157 patients (95 percent), with complete eradication of intestinal metaplasia in 137 (83 percent). Among those with complete eradication of intestinal metaplasia, recurrent intestinal metaplasia was detected in 48 (35 percent), with dysplasia in 12 (9 percent). Among the patients who had eradication of neoplasia but not complete eradication of intestinal metaplasia, recurrent dysplasia was detected in 6 of 19 (32 percent). Neoplasia (dysplasia or carcinoma) was more likely to recur in patients who had multifocal dysplasia and who were older, whereas neoplasia was less likely to occur in patients who had complete eradication of intestinal metaplasia.

- **Radiofrequency ablation** – RFA uses radiofrequency energy delivered by a balloon or paddle-shaped device that has a series of closely spaced electrodes to ablate the Barrett's mucosa [111]. RFA rapidly generates a uniform thermal injury with limited depth. For patients with visible mucosal irregularities associated with dysplasia, endoscopic resection should be performed prior to RFA. A number of well-designed studies, including a randomized, sham-controlled trial, suggest that RFA is highly effective at removing all Barrett's epithelium at both the endoscopic and histologic level with a favorable safety profile. Studies also suggest that RFA reduces the risk of malignant progression. In one randomized trial, patients with low- or high-grade dysplasia who underwent RFA were less likely to progress to higher grades of dysplasia or cancer than patients who underwent sham-therapy (4 versus 16 percent) [114]. (See "Barrett's esophagus: Treatment with radiofrequency ablation", section on 'Efficacy'.)

  In a meta-analysis of 20 studies, complete eradication of dysplastic Barrett's mucosa was achieved in 91 percent of patients [115]. Similarly, in a systematic review that included 12 studies of RFA for the eradication of high-grade dysplasia or early cancer in patients with Barrett's esophagus, RFA (preceded by endoscopic resection of nodular disease if necessary) resulted in eradication of high-grade dysplasia or early cancer in 92 percent and complete eradication of Barrett's esophagus in 88 percent [116].

  Although initial studies suggested that recurrences were uncommon, subsequent studies have documented considerably higher rates of recurrence, underscoring the need for ongoing surveillance following RFA. For example, a study of 246 patients with high-grade dysplasia or intramucosal carcinoma described initial complete eradication of all intestinal metaplasia in 80 percent of cases. However, neoplasia (dysplasia or cancer) recurred at a rate approaching 25 percent after 60 months, and metaplasia recurred at a rate approaching 50 percent by 48 months [117]. In a study of 218 patients who had achieved

complete eradication of Barrett's metaplasia with RFA, 52 patients (24 percent) had recurrence of metaplasia or Barrett's-associated neoplasia over 541 person-years of follow up (incidence rate of 9.6 percent per year) [118]. Another report suggested that, following complete eradication of Barrett's esophagus, intestinal metaplasia recurred at a rate of 8 to 10 percent per patient-year, and dysplasia recurred at an annual rate of 2 to 3 percent [119]. (See "Barrett's esophagus: Treatment with radiofrequency ablation" and 'Endoscopic resection' below.)

- **Endoscopic cryotherapy** – Endoscopic cryotherapy is a technique for ablation of Barrett's mucosa. A cryotherapy system is used to apply a cryogen such as liquid nitrogen or liquid nitrous oxide endoscopically to the Barrett's esophagus. The resultant rapid freezing and thawing of the Barrett's tissue disrupts cell membranes, induces apoptosis, and causes thrombosis of local blood vessels. Observational studies suggest that cryotherapy eradicates high-grade dysplasia in approximately 95 to 100 percent of patients, all dysplasia in 85 to 90 percent, and all intestinal metaplasia in 55 percent [120-123]. However, very little long-term data are available, and RFA remains the most commonly used ablation technique.

  Unlike RFA that uses heat to denature cellular proteins, cryoablation induces intracellular ice crystal formation that causes no permanent change in protein structure, thus preserving the extracellular collagen matrix architecture. In theory, this may result in less stricture formation with cryotherapy compared with RFA, but the clinical advantage of cryotherapy in this regard is not yet established.

  - In an analysis of 60 patients with Barrett's esophagus and high-grade dysplasia who completed all of their planned cryotherapy sessions, 58 (97 percent) had complete eradication of high-grade dysplasia, 52 (87 percent) had complete eradication of all dysplasia, and 34 (57 percent) had complete eradication of all Barrett's mucosa [120]. Subsquamous ("buried") Barrett's mucosa was found in two patients (3 percent). Complications included chest pain (two patients) and strictures (three patients). One patient developed bright red blood per rectum following the procedure. There were no esophageal perforations.

  - In a second series, 32 patients with Barrett's esophagus and high-grade dysplasia were treated with cryotherapy [121]. If high-grade dysplasia recurred, additional therapy was performed. At two years of follow-up, 32 patients (100 percent) had complete eradication of high-grade dysplasia, and 27 patients (84 percent) had complete eradication of Barrett's mucosa. High-grade dysplasia recurred in six patients (19 percent). Among those with recurrent high-grade dysplasia, five were treated with

repeat cryotherapy (four patients) or argon plasma coagulation (one patient) and were free from high-grade dysplasia at their most recent follow-up (range 24 to 57 months). The sixth patient progressed to adenocarcinoma but was treated with cryotherapy, with subsequent downgrading of the lesion to high-grade dysplasia.

- In a third series with 64 patients with Barrett's esophagus and high-grade dysplasia or early adenocarcinoma, endoscopic mucosal resection of visible lesions followed by cryotherapy led to complete response rates of 77 percent for cancer (10 of 13), 94 percent for high-grade dysplasia (60 of 64), 89 percent for all dysplasia (57 of 64), and 55 percent for intestinal metaplasia (35 of 64) [122].

After endoscopic ablation by any technique, patients are given a proton pump inhibitor (if not already on one) so that the injured mucosa heals with the growth of new squamous epithelium. The relative merits of the various endoscopic ablative therapies are disputed. One major concern is that the procedures may not eradicate all of the dysplastic cells. Partially ablated metaplastic mucosa can heal with an overlying layer of squamous epithelium that hides the "buried" metaplastic tissue from the endoscopist (picture 2), and adenocarcinomas have developed from these residual deposits of metaplasia [124].

Surveillance after ablative therapy — Follow-up endoscopic surveillance after ablative therapy will depend on the initial grade of dysplasia and whether there is complete eradication of intestinal metaplasia. This is discussed separately. (See "Barrett's esophagus: Treatment with radiofrequency ablation", section on 'Follow-up endoscopy'.)

Endoscopic resection — Endoscopic resection includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Endoscopic resection involves the excision of a large segment of esophageal mucosa down to the submucosa [125,126]. Unlike the endoscopic ablative techniques that merely destroy tissue, endoscopic resection provides large tissue specimens that can be examined by the pathologist to determine the character and extent of the lesion and the adequacy of resection. Therefore, it can provide important staging information (revealing submucosal invasion that might not be apparent by less invasive techniques and that would require esophagectomy or other modalities for cure) and be therapeutic as well (if there is no submucosal extension). Endoscopic resection can also be combined with endoscopic ablative therapies for the eradication of Barrett's mucosa in patients who have visible lesions. (See "Overview of endoscopic resection of gastrointestinal tumors" and "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection".)

In a systematic review that included 11 studies of patients with Barrett's esophagus who underwent EMR, complete eradication of high-grade dysplasia or early esophageal adenocarcinoma was achieved in 95 percent of patients, and complete eradication of all Barrett's mucosa was achieved in 89 percent [116].

Endoscopic resection of the entire Barrett's mucosa is usually not recommended because of the high rate of stricture formation after circumferential resections. In a study of 47 patients with ≤5 cm of Barrett's mucosa containing high-grade dysplasia or early cancer, stepwise radical endoscopic resection (in which endoscopic resection is repeated with the goal of eradicating all of the Barrett's mucosa) was compared with endoscopic resection of visible mucosal irregularities followed by RFA [127]. Both groups had high rates of complete remission of both neoplasia and intestinal metaplasia (ranging from 96 to 100 percent and 92 to 96 percent, respectively), but the stenosis rate was significantly higher in the patients who underwent stepwise radical endoscopic resection (88 versus 14 percent).

It is important to note that most of the studies of endoscopic resection for eradication of Barrett's esophagus have come from highly specialized centers, and it is not clear that these results can be duplicated in a community setting [128]. Furthermore, recurrent neoplasms develop frequently after endoscopic therapy, especially if the residual Barrett's epithelium is not eradicated. (See "Barrett's esophagus: Treatment of high-grade dysplasia or early cancer with endoscopic resection".)

Esophagectomy — Esophagectomy is the only therapy for high-grade dysplasia that removes all of the neoplastic epithelium along with any occult malignancy and regional lymph nodes. However, it also has the highest rates of procedure-related mortality and long-term morbidity. The mortality rates for esophagectomy among institutions vary inversely with the frequency with which the operation is performed. In a study of data from the Dutch National Medical Registry, the mortality rates for esophagectomy were 12.1, 7.5, and 4.9 percent at centers performing 1 to 10, 11 to 20, and more than 50 esophagectomies per year, respectively [129]. With the development of effective endoscopic therapies, esophagectomy can now be avoided for most patients with high-grade dysplasia in Barrett's esophagus.

The average hospital stay for open esophagectomy is approximately two weeks, and 30 to 50 percent of patients develop at least one serious postoperative complication such as pneumonia, arrhythmia, myocardial infarction, heart failure, wound infection, or anastomotic leak [129-132]. Esophagectomy is frequently associated with long-term problems such as dysphagia, weight loss, gastroesophageal reflux, and dumping. Some of these complications are related to transection of the vagal nerve and may be reduced with a vagal-sparing esophagectomy [133].

Minimally invasive techniques for esophagectomy are being increasingly described. Initial experience (mainly from high-volume centers) has suggested that the minimally invasive techniques are associated with similar postoperative morbidity and mortality rates but with reduced blood loss, postoperative pain, and intensive care unit stay [134]. Their role in the management of Barrett's esophagus with high-grade dysplasia continues to be defined, although they may be an option in centers with appropriate expertise.

One advantage of esophagectomy over endoscopic eradication is that occult lymph node metastases can be detected. However, lymph node metastases occur in only one to two percent of patients with high-grade dysplasia or intramucosal carcinoma in Barrett's esophagus, and this rate of metastatic disease is lower than the mortality rate associated with esophagectomy [135]. In addition, esophagectomy does not guarantee cure for a tumor that already has metastasized to the lymph nodes. A systematic review looked at the frequency of lymph node metastases in patients with mucosal neoplasms in Barrett's esophagus who underwent esophagectomy [135]. The review included 70 studies with 1874 patients who underwent esophagectomy with lymph node dissection for high-grade dysplasia or intramucosal carcinoma. Overall, lymph node metastases were identified in the resection specimen from 26 patients (1.4 percent). When evaluated based on the final pathologic diagnosis, there were no metastases in the 524 patients with high-grade dysplasia, and metastases were found in 26 of the 1350 patients (1.9 percent) with intramucosal carcinoma.

Management of invasive esophageal adenocarcinoma — Patients with invasive adenocarcinoma of the esophagus (into the submucosa and beyond) should be referred to an oncologist for staging and to discuss treatment options. The choice of treatment will depend on the patient's overall health and the stage of the cancer and may include chemoradiotherapy with or without esophagectomy, or even endoscopic resection in highly selected cases. (See "Management of superficial esophageal cancer", section on 'Initial assessment'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Barrett's esophagus".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Barrett's esophagus (The Basics)")
- Beyond the Basics topics (see "Patient education: Barrett's esophagus (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Cancer risk** – The risk of developing esophageal adenocarcinoma in patients with nondysplastic Barrett's esophagus is estimated to be 0.1 to 0.4 percent per year. Although this risk is increased at least 30-fold above that of the general population, the absolute risk for any individual patient with nondysplastic Barrett's esophagus is low. (See 'Cancer risk' above.)
- **Medical therapy** – We suggest that all patients with Barrett's esophagus receive treatment with a proton pump inhibitor (PPI) rather than reserving treatment only for patients who are symptomatic (**Grade 2B**). We typically start patients on a PPI once daily, and only increase the dose if it is required to eliminate gastroesophageal reflux disease symptoms or to heal reflux esophagitis. (See 'Management of acid reflux' above.)
- **Endoscopic surveillance and subsequent management** – In patients with suspected Barrett's esophagus, we perform endoscopic four-quadrant biopsies every 2 cm and wide-area transepithelial sampling with computer-assisted 3-dimensional analysis (WATS-3D). Any mucosal irregularities in the Barrett's segment should be removed with endoscopic resection, and the resected specimen should be sent for evaluation by a pathologist with expertise in esophageal histopathology. Subsequent management depends on whether dysplasia is seen on histology (algorithm 1) (see 'Surveillance' above):

- **Nondysplastic Barrett's esophagus** – For patients with nondysplastic Barrett's esophagus, we perform surveillance endoscopy, and the length of the nondysplastic Barrett's segments generally informs the intervals for endoscopic surveillance. Patients with longer segments (≥3 cm) undergo surveillance every three years, whereas patients with shorter segments (<3 cm) undergo surveillance every five years.

  If the biopsies show no dysplasia, we discuss with the patient the potential risks and benefits of surveillance. Some of the potential harms include a decrease in quality of life due to worry about cancer development, the risks associated with endoscopy, the risks and morbidity associated with invasive therapies used to treat lesions identified by surveillance, and missed lesions despite surveillance. A well-informed patient with nondysplastic Barrett's esophagus may reasonably choose not to undergo surveillance despite endorsement of the practice by gastrointestinal societies. A discussion of the risks and benefits of surveillance should be well documented in the patient's medical record, particularly if the patient elects to not undergo surveillance.

- **Low-grade dysplasia** – A finding of low-grade dysplasia on biopsies should be confirmed by a pathologist with expertise in Barrett's esophagus-related neoplasia. Four quadrant biopsy specimens should be obtained at 1 cm intervals, and any mucosal irregularities should be removed with endoscopic resection. If such specimens were not obtained during the endoscopy that revealed low-grade dysplasia, then endoscopy should be repeated as soon as feasible to ensure that the metaplastic mucosa is adequately inspected and biopsied appropriately before proceeding to endoscopic eradication.

  If low-grade dysplasia is confirmed, we suggest endoscopic eradication therapy rather than expectant management with ongoing surveillance (**Grade 2B**). (See 'Low-grade dysplasia' above.)

  Our preference for endoscopic eradication therapy is endoscopic resection of any visible mucosal irregularities, followed by radiofrequency ablation (RFA) to ablate the remaining metaplastic epithelium (provided the resected specimen shows no submucosal invasion). This approach is effective and has a good safety profile. The frequency of subsequent surveillance will depend on whether all intestinal metaplasia is eradicated. (See 'Endoscopic ablative therapies' above.)

  If the patient does not undergo endoscopic eradication for low-grade dysplasia, surveillance endoscopy should be performed every six months for one year with

biopsies every 1 cm and then annually until there is reversion to nondysplastic Barrett's.

- **Indefinite for dysplasia** – If the initial biopsies are indefinite for dysplasia, we optimize medical antireflux therapy (eg, prescribing a PPI twice daily, ensuring compliance with PPI therapy, ensuring that the PPI is taken correctly). Antireflux therapy minimizes reactive esophageal changes due to reflux esophagitis that may be mistaken for dysplastic changes. After antireflux therapy has been optimized, we repeat an endoscopy with biopsy specimens taken every 1 cm. We typically perform the endoscopy after two months of treatment (to allow sufficient time for healing). Repeat endoscopy should not be delayed beyond six months. Any mucosal irregularities should be removed with endoscopic resection.

  If the repeat biopsies still are indefinite for dysplasia, the diagnosis should be confirmed by a pathologist with expertise in esophageal histopathology. If the diagnosis is confirmed, management options include surveillance endoscopy every 12 months or referral of the patient to a center with expertise in managing patients with Barrett's esophagus.

- **High-grade dysplasia or intramucosal carcinoma** – For patients found to have high-grade dysplasia or intramucosal carcinoma, biopsy specimens should be obtained at 1 cm intervals, and any mucosal irregularities should be removed with endoscopic resection. If biopsy specimens were not obtained at 1 cm intervals or a mucosal irregularity was not removed with endoscopic resection, endoscopy should be repeated as soon as possible to obtain these specimens. A finding of high-grade dysplasia or intramucosal carcinoma on biopsies should be confirmed by a pathologist with expertise in esophageal histopathology.

  If high-grade dysplasia or intramucosal carcinoma is confirmed, and there is no evidence of submucosal invasion in the resected specimens, we suggest endoscopic eradication therapy rather than esophagectomy (**Grade 2B**).

  The frequency of subsequent surveillance will depend on whether all intestinal metaplasia is eradicated. (See 'Endoscopic ablative therapies' above and "Barrett's esophagus: Treatment with radiofrequency ablation", section on 'Follow-up endoscopy'.)

  Our approach to endoscopic eradication therapy is to perform endoscopic resection of any visible mucosal irregularities, followed by RFA to ablate the remaining metaplastic

epithelium. (See 'Endoscopic resection' above and 'Endoscopic ablative therapies' above.)

- **Adenocarcinoma** – Patients with invasive adenocarcinoma of the esophagus should be referred to an oncologist for staging and to discuss treatment options, and this is discussed separately. (See "Management of superficial esophageal cancer", section on 'Initial assessment'.)

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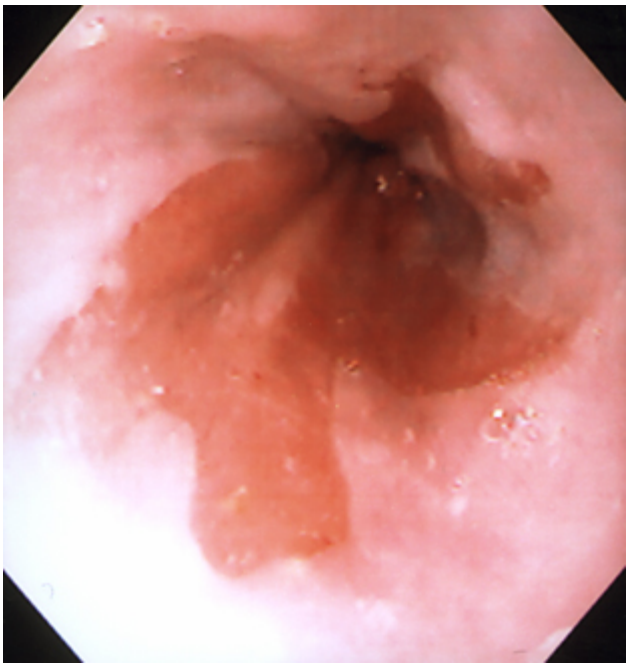
Topic 2236 Version 65.0

GRAPHICS

Barrett's esophagus

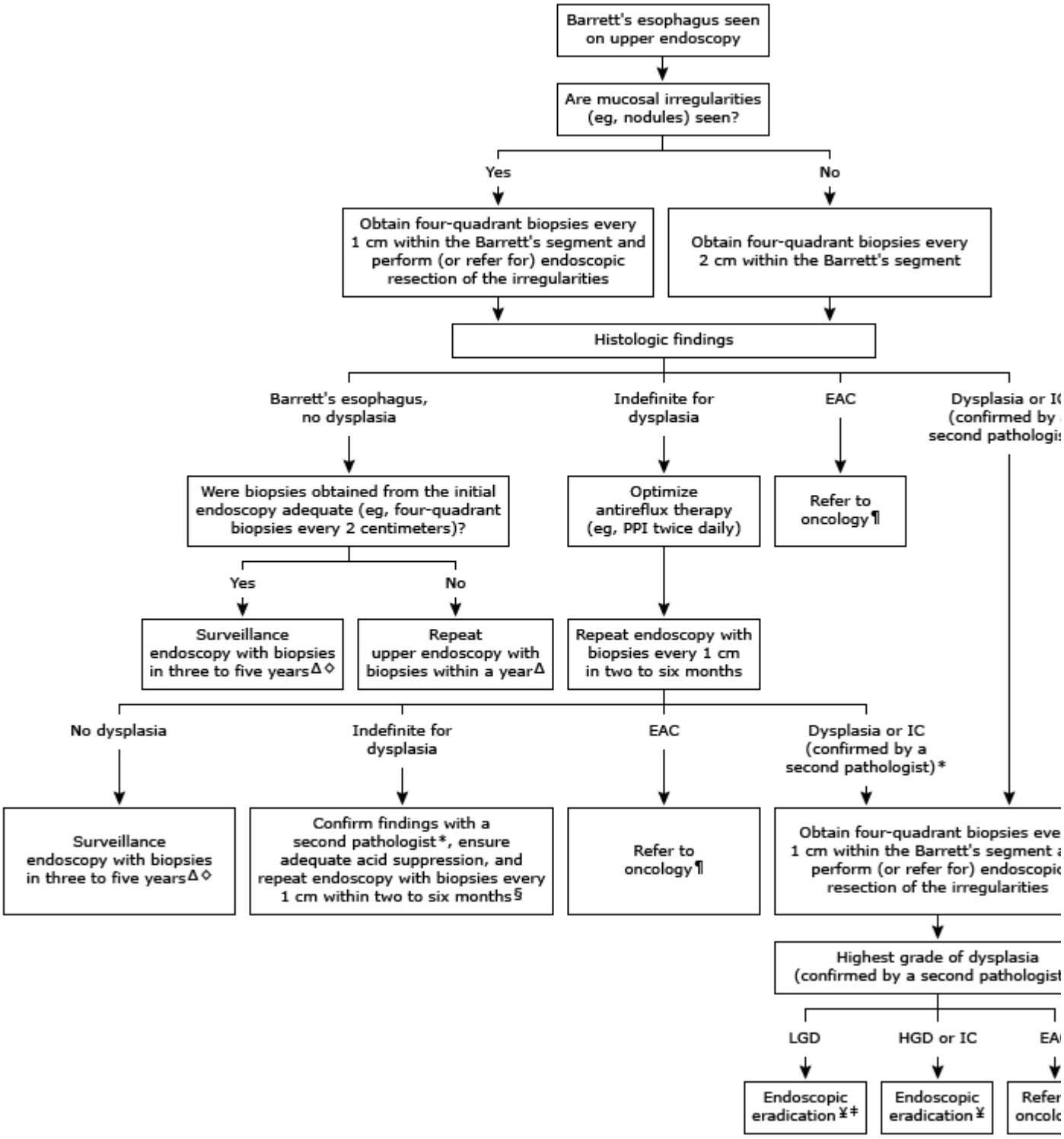


Endoscopic view of Barrett's esophagus prior to treatment. The salmon-colored tongues of Barrett's mucosa are visible in the background of the the pale, pink squamous mucosa.

Courtesy of Marta Davila, MD and Jacques Van Dam, MD, PhD.

Graphic 62689 Version 1.0

Surveillance and management of Barrett's esophagus



IC: intramucosal carcinoma; EAC: esophageal adenocarcinoma; PPI: proton pump inhibitor; LGD: low-grade dysplasia; HGD: high-grade dysplasia.

* The pathologists should have expertise in esophageal histopathology.

¶ The choice of treatment will depend on the patient's overall health and the stage of the cancer, and may include chemoradiotherapy with or without esophagectomy, or even endoscopic resection in highly selected cases.

Δ Subsequent management will depend on whether dysplasia is present on surveillance biopsies.

◇ The length of the nondysplastic Barrett's segments generally informs the intervals for endoscopic surveillance. Patients with longer segments (≥3 cm) undergo surveillance every three years, whereas patien with shorter segments (<3 cm) undergo surveillance every five years.

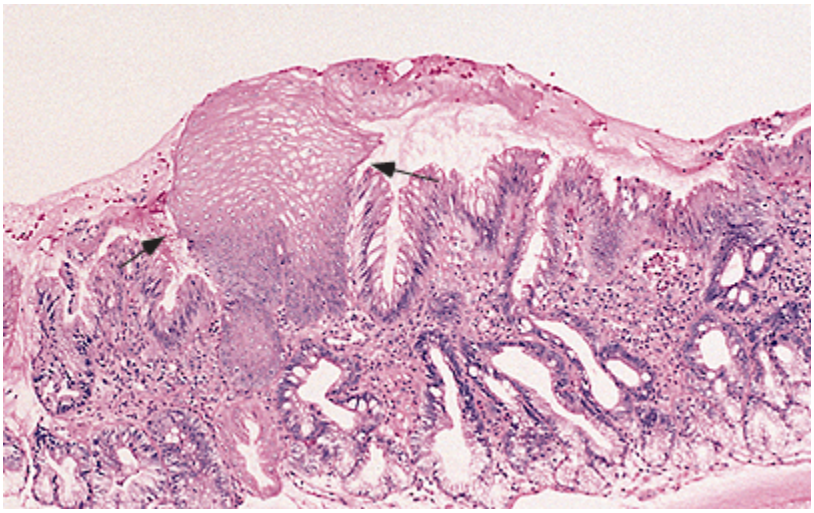
§ If the biopsies again are indefinite for dysplasia, initiate surveillance every 12 months or refer the patient t center that specializes in the management of patients with Barrett's esophagus.

¥ Options for endoscopic eradication therapy include radiofrequency ablation and spray cryotherapy. The choice of therapy will depend on local expertise. Esophagectomy is an alternative if endoscopic eradication therapy is not available.

‡ Patients who do not undergo endoscopic eradication should undergo endoscopic surveillance every 6 mor for one year with biopsies obtained at 1 cm intervals and then annually until there is reversion to nondyspla Barrett's.

Graphic 103792 Version 4.0

Barrett's esophagus beneath squamous mucosa



Low power view demonstrates the glandular epithelium of Barrett's esophagus with an island of overlying squamous mucosa (arrows). Larger areas of squamous mucosa may render underlying Barrett's esophagus inapparent on endoscopy. This has been a concern in patients treated by some forms of ablative therapy in which replacement of columnar epithelium by squamous epithelium may not obviate the risk of malignant transformation from underlying Barrett's mucosa.

From: Lewin KJ, Appelman HD. Tumors of the esophagus and stomach. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 18, 1996, Washington, DC. Armed Forces Institute of Pathology.

Graphic 78238 Version 3.0

Contributor Disclosures

Stuart J Spechler, MD Consultant/Advisory Boards: Castle Biosciences [Barrett's esophagus]; Interpace Diagnostics [Barrett's esophagus]; Ironwood Pharmaceuticals [GERD]; ISOThrive, LLC [GERD]; Phathom Pharmaceuticals [GERD]; Takeda Pharmaceuticals [GERD]. All of the relevant financial relationships listed have been mitigated. **Nicholas J Talley, MD, PhD** Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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